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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,327	06/21/2006	Michel Schneider	BR-035 PUS 01	4727

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
06/06/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,327	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *16,17,25,26,31-40,43 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,18-24,27-30,41,42 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/20/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 1/31/2011, in reply to the Office Action mailed 8/03/2010, is acknowledged and has been entered. Claims 1-45 are pending, of which claims 31-40, 43 and 44 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 16, 17, 25 and 26 are withdrawn from consideration as being drawn to non-elected species. Claims 1-15, 18-24, 27-30, 41, 42 and 45 are readable upon the elected invention and species and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments, with regard to the double patenting rejection over the claims of copending USSN 10/584,382 have been fully considered. The rejection is withdrawn in view of abandonment of the '382 application.

Applicant's arguments, with regard to the rejection of claims 1, 4-15, 18, 19, 27-30 and 42 under 35 U.S.C. 103(a) as being unpatentable over Eriksen (US 2004/0146462) have been fully considered. The rejection is withdrawn because Eriksen does not teach particle size of 100 nm or lower, as required by the instant claims, but rather teaches "greater than 0.1 micron."

Applicant's arguments, with regard to the rejection of claims 1-15, 18-24, 27-30, 41, 42 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Schneider *et al.* (US 6, 258,378) in view of Eriksen *et al.* (US 2004/0146462), in further view of Unger (US 2002/0159952), have been fully considered. The rejection is withdrawn because Schneider does not specifically recite liposome particle size as less than 100 nm. New grounds of rejection are set forth herein in view of newly discovered prior art references.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-12, 18, 19, 27-30, 41, 42 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2000143550 in view of WO 03/05029.

JP 2000143550 teaches magnetic substance particles (preferably Fe_2O_3, Fe_3O_4, etc.) are adsorbed onto the surfaces of microbubbles coated with a carboxylic acid salt

(preferably sodium laurate, etc.). The contrast medium is preferably used by coating the magnetic substance particles with a cationic surfactant. The movement of the contrast medium can be controlled by external magnetic field. Thereby, the microubbles can timely be introduced into sites causing problems in the human body, e.g. specific regions such as tumors in various kinds of internal organs or early cancers and diseases can accurately be observed and diagnosed by ultrasonic waves (abstract). See also paragraphs 0014-0028 for working examples, association between including magnetite particles with cationic surfactant (e.g. DCPL) coating and sodium stearate microbubbles in aqueous solution.

The magnetic particles electrostatically associated with the microbbles in the example of JP 2000143550 are 300 nm, rather than 100 nm or less, as claimed.

WO 03/05029 teaches superparamagnetic nanoparticles of magnetite. Particles are highly crystalline in the 10-250, preferably 50 to 150 nm diameter range, exhibiting superparamagnetic characteristics with a saturation magnetization of 62 emu/g. The particles are stabilized with a coating such as dextran. These particles have potential applications in biological cell separations, drug delivery, and nondestructive clinical diagnosis (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify particle size of the magnetic particles taught by JP 2000143550 which are used for magnetically guiding microbubbles, to employ a particle size such as 50 nm. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because WO 03/05029 shows that particles in the

range of 50-150 nm are preferable for use in magnetic drug delivery or biological cell separation.

Regarding claim 4, iron oxide nanoparticles may also serve as a diagnostic agent for MRI.

Regarding claims 5-6, Na+ is present.

Regarding claims 9-11, it would have been obvious to one of ordinary skill to optimize ratio of microbubble:magnetic particle as a matter of routine experimentation. Differences in concentration or temperature will generally not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); *In re Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382; or *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969).

Regarding claims 28-30, with respect to the claimed zeta potential, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The claims are descriptive and thus would be an inherent property of the claimed composition. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat.

App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). In the instant case, since the compositions of 2000143550 teaches incorporation of the claimed structural elements of the claims, it is interpreted absent evidence to the contrary that the compositions would be capable of inherently meeting the claimed zeta potential.

Claims 1-12, 18-24, 27-30, 41, 42 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2000143550 in view of WO 03/05029, in further view of Bao (US 2005/0130167).

The rejection over JP 2000143550 in view of WO 03/05029 is applied as above.

It would have been obvious to provide a micelle coating on iron oxide nanoparticles when the teaching of JP 2000143550 and WO 03/05029 are taken in view of Bao.

Bao teaches multifunctional magnetic nanoparticle probes for intracellular molecular imaging and monitoring (paragraph 0015). The coating material on the magnetic nanoparticle self assemble to form the biocompatible coating. As used herein, a "coating material" refers to a dextran molecule, a dendrimer, an amphiphilic polymer/bio-polymer (e.g. phospholipid, peptide etc.), a polymer, a surfactant, or chemical compound with chelating properties for a magnetic nanoparticle or high affinity for adsorption on a magnetic nanoparticle. In further preferred embodiments, these self-assembled coating materials form a micelle, liposome, or dendrimer shaped structure (paragraph 0047). See also paragraph 0171, drawn to micelle-MIONs having

a coating comprising a phospholipid-polyethylene glycol (PEG) molecule. Mixtures of 1,2-Distearoyl-sn-Glycero-3-Phosphoethanolamine Polyethylene Glycol 2000 (DSPE-PEG 2000) and 1,2-Distearoyl-sn-Glycero-3-Phosphoethanolamine-N-[Amino(Polyethylene Glycol) 2000] (DSPE-PEG 2000 Amine) surfactants are used as coating, referred to as micelle. This coating provides biocompatibility and enhances solubility of the MIONs. It also has the added advantage of flexible functionality, since a number of modified PEGs other than PEG-amine are readily available (e.g. PEG-maleimide).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide a micelle coating on iron oxide nanoparticles taught in the compositions of JP 2000143550, as shown by Bao. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Bao teaches that micelle coatings, such as those containing PEG-modified phospholipid (e.g. phosphoethanolamine), provide the advantage of biocompatibility and enhancing solubility of the MIONs, as well as the added advantage of flexible functionality, since a number of modified PEGs other than PEG-amine are readily available coating and provide biocompatibility and enhances solubility of the MIONs.

Claims 1-15, 18, 19, 27-30, 41, 42 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2000143550 in view of WO 03/05029, in further view of Dugstad (US 6,221,337).

The rejection over JP 2000143550 in view of WO 03/05029 is applied as above.

It would have been obvious to substitute a negatively charged phospholipid stabilized microbubble for the negatively charged fatty acid stabilized microbubbles when the teachings of JP 2000143550 in view of WO 03/05029 are taken in view of Dugstad.

Dugstad teaches microbubbles surrounded by a monolayer of negatively charged phospholipids as contrast agents for ultrasonic imaging. It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute a phospholipid stabilized microbubble bearing negative overall charge as functionally equivalent to the fatty acid stabilized microbubbles taught by JP 2000143550. One would have been motivated to do so because Dugstad teaches that both fatty acids and negatively charged phospholipids, such as phosphatidylserine, are known for stabilizing microbubbles for ultrasonic imaging (column 3), and teaches that phosphatidylserine-based contrast agents have advantages such as desirable properties with respect to elimination from blood stream (column 4, lines 60+). One would have had a reasonable expectation of success in doing so because both phospholipid or fatty acid bearing negative charge would be expected to be capable of electrostatic interaction with cationic surfactant on magnetic particle.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-

9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS

/MICHAEL G. HARTLEY/
Supervisory Patent Examiner, Art Unit 1618